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Bortezomib Plus Dexamethasone Followed by Escalating Donor Lymphocyte Infusions for Patients with Multiple Myeloma Relapsing or Progressing after Allogeneic Stem Cell Transplantation

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A B S T R A C T

Multiple myeloma relapsing after allogeneic stem cell transplantation (alloSCT) has a poor outcome. To assess the safety and efficacy of bortezomib and dexamethasone (VD) combination followed by donor lymphocyte infusions (DLIs) in myeloma patients relapsing or progressing after alloSCT, a prospective phase II study was designed. The treatment plan consisted of three VD courses followed by escalated doses of DLIs in case of response or at least stable disease. Nineteen patients were enrolled with a median age of 57 years (range, 33 to 67); 14 patients were allografted from human leukocyte antigen–identical siblings and 5 from alternative donors. Sixteen of 19 patients received the planned treatment, but 3 patients did not: 2 patients because of disease progression and 1 refused. After the VD phase the response rate was 62%, with 1 complete remission, 6 very good partial remissions, 5 partial remissions, 2 patients with stable disease, and 5 with progressive disease. After the DLI phase, the response rate was 68%, but a significant upgrade of response was observed: 3 stringent complete remissions, 2 complete remissions, 5 very good partial remissions, 1 partial remission, 4 with stable disease, and 1 with progressive disease. With a median follow-up of 40 months (range, 29 to 68), the 3-year progression-free survival and overall survival rates were 31% and 73%, respectively. Neither unexpected organ toxicities, in particular severe neuropathy, nor severe acute graft-versus-host disease flares were observed. VD-DLIs is a safe treatment for multiple myeloma patients relapsing or progressing after alloSCT and may be effective.

INTRODUCTION

The natural history of multiple myeloma (MM) is characterized by periods of disease control and subsequent recurrence. Therefore, the use of multiple lines of treatment is common in the clinical management. Allogeneic stem cell transplantation (alloSCT) represents an option for young patients with an available donor; however, a significant fraction of patients relapse [1–4]. Despite the evidence of long-lasting remissions, myeloablative conditioning regimens have been a matter of concern due to high transplant-related mortality, sometimes offsetting the survival benefit. The introduction of reduced intensity and nonmyeloablative conditioning regimens allowed a toxicity reduction with the retention of the graft-versus-myeloma (GVM) effect [3–5]. The GVM effect represents an important therapeutic component of alloSCT; thus, donor lymphocyte infusions (DLIs) have been used to treat relapse or progression. DLIs alone are able to induce responses in the range of 30% [6], with the most relevant treatment-related morbidity represented by the occurrence of graft-versus-host disease (GVHD) (40% to 50%). The use of DLIs at escalating doses had the most favorable profile in terms of antimyeloma activity and low incidence of acute GVHD (aGVHD) [7]. Relapse after alloSCT is particularly challenging, because patients are frequently frail, due to late-onset transplant-related complications [8], and their disease is often chemoresistant [9].

Bortezomib represents an attractive drug for MM treatment after alloSCT, because its toxicity profile does not overlap with the most common complications occurring after alloSCT. Bortezomib has been extensively studied in the context of relapse/progression after autologous SCT, showing a response rate ranging from 35% [10] to 43% [11]. After alloSCT, only few data from retrospective studies are available.

Interestingly, bortezomib has several immune modulatory activities. It has been shown to sensitize target cells to immune-mediated killing through TRAIL/DR5 and Fas/FasL pathways on natural killer and CD8 T effector cells [12]. Bortezomib treatment can also lead to down-regulation of

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cell surface expression of human leukocyte antigen (HLA) I, promoting natural killer activity. Moreover, its direct cytotoxic effect may increase the immunogenicity of the dying cells, resulting in further in vivo expansion of the antitumor immune response [13,14]. On the other hand, bortezomib can suppress the immune function by down-regulating pro-inflammatory cytokines, inhibiting dendritic cell maturation [15], and killing highly activated lymphocytes [16]. Because there are no prospective studies assessing the efficacy of bortezomib after alloSCT and considering the GVM associated with DLI, we conducted a prospective phase II study on the use of bortezomib and dexamethasone (VD) for myeloma cytoreduction before DLIs.

METHODS

Study Design

This is a phase II, multicentric, prospective pilot study evaluating the efficacy and safety of 3 VD courses followed by escalating doses of DLIs in relapsed or progressing MM. The trial was conducted at four Italian hematology centers between 2007 and 2010. The study was approved by the ethics committee of all the participating centers and coordinated by the Fondazione Michelangelo, in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. All patients gave informed consent to the treatment and the analysis of outcome data. The study was registered to European health authorities with the EudraCT number: 2006-004815-24.

The study enrolled MM patients age 18 to 70 years with measurable disease relapsing or progressing $\geq$100 days after alloSCT and still untreated for their relapse. For the enrollment the discontinuation of immunosuppressive therapy at least 5 weeks before enrollment was required. Patients were excluded in case of active GVHD or ongoing treatment with immunosuppressive drugs, or if they had contraindications to bortezomib treatment.

Patients

Nineteen patients with relapsed or progressing MM after alloSCT were enrolled. Median age was 57 years (range, 33 to 67 years). At diagnosis, 16 patients had International Staging System (ISS) stage I MM, 2 had ISS stage II, and 1 had ISS stage III MM. Before alloSCT, the median number of previous lines of treatment was 2 (range, 2 to 5 lines); 4 patients had already received bortezomib before alloSCT. All patients received a previous autologous SCT. Median time from diagnosis to alloSCT was 19 months (range, 8 to 52 months). The conditioning regimens were nonmyeloablative in 6, reduced intensity in 11, and myeloablative in 2 patients. In all cases, peripheral blood stem cells were infused. Two patients had G1 sensory peripheral neuropathy at enrollment. Median time between alloSCT and enrollment was 55 months (range, 8 to 145 months). Patient characteristics are summarized in Table 1.

Table 1
Patient Characteristics

Characteristic	Value
Age, yr, median % (range)	57 (33–67)
Male	11 (58)
ISS at diagnosis, no. of patients	
I	16 (84)
II	2 (10)
III	1 (6)
Lines of treatment before VD-DLI (range)	2 (2–5)
Bortezomib treatment before alloSCT, no. of patients	4
Previous autologous SCT	19 (100)
Median time from diagnosis to alloSCT, months (range)	19 (8–52)
Conditioning regimens	
TBI 2 Gy based	6 (32)
Thiotepa-fludarabine based	6 (32)
Fludarabine-melphalan based	3 (16)
Busulfan or TBI 9 Gy based	4 (20)
Nonmyeloablative	6 (32)
Reduced intensity	11 (58)
Myeloablative	2 (10)
Donors	
HLA-identical siblings	14 (74)
Single antigen mismatched sibling	2 (10)
Matched unrelated donors	3 (16)
GVHD before enrollment	
aGVHD	3 (16)
cGVHD	6 (32)
Median time from alloSCT to enrollment, months (range)	55 (8–145)
Peripheral neuropathy before enrollment, no. of patients	2 (10, grade 1)

TBI indicates total body irradiation; Gy, Gray.
Values are n (%) unless otherwise noted.

Treatment Plan

Treatment consisted of three 21-day courses with intravenous bortezomib 1.3 mg/m^2 at days 1, 4, 8, and 11 and oral dexamethasone 20 mg/day at days 1 to 2, 4 to 5, 8 to 9, and 11 to 12. Fourteen days after the third course of bortezomib-dexamethasone, in absence of active aGVHD chronic GVHD (cGVHD), the DLI program was started. DLIs were administered every 6 weeks at escalating cell doses, up to 4 infusions. For transplants from HLA-identical siblings, the infusions were done at the following cell doses: 5×10^6 CD3+/kg, 1×10^7 CD3+/kg, 5×10^7 CD3+/kg, and 1×10^8 CD3+/kg. For transplants from HLA-mismatched siblings or matched unrelated donors, the infusion scheme consisted of 5×10^5 CD3+/kg, 1×10^6 CD3+/kg, 5×10^6 CD3+/kg, and 1×10^7 CD3+/kg. In case of complete remission (CR) achievement after the VD phase, the patients received only the first 2 DLI doses. The DLI program was stopped in case of aGVHD or cGVHD occurrence. All patients received prophylaxis for herpes viruses with valacyclovir 500 mg or 1000 mg twice daily, or with acyclovir 400 mg or 800 mg twice daily, according to renal function.

Disease Monitoring

Disease response was assessed according to the IMWG criteria [17]. Serum and urine chemistry were evaluated at the following time points: at enrollment, after each VD, after each DLI, and monthly after the last DLI for 1 year. Bone marrow biopsy was performed at enrollment, after the VD and DLI phases, and every 3 months for 1 year after the last DLI. Magnetic resonance imaging was obtained at enrollment, after the VD and the DLI phases, and 12 months after the last DLI. X-ray skeletal survey was obtained at enrollment and at 12 months after the last DLI. Chimerism was assessed on DNA extracted from peripheral blood samples by multiplex fluorescent short-tandem repeat analysis (AmpFISTR Profiler Plus PCR kit, Applied Biosystems, Foster City, CA). Direct flow cytometric immunophenotyping was performed to analyze lymphocyte subsets, including CD3+/CD4+, CD3+/CD8+, CD20+, and CD16+/CD56. All antibodies were obtained from BD Biosciences (San Jose, CA). Samples were analyzed using the FACSCalibur flow cytometer (BD Biosciences). Immunophenotyping was performed at study enrollment, after the VD phase, and at 3, 6, 9, and 12 months after the last DLI. Molecular minimal residual disease was done on bone marrow samples as previously described [18] in patients who obtained at least a CR at the following time points: after the VD and DLI phases, and at 3, 6, 9, and 12 months after the last DLI.

Statistics

The primary objective of the study was the efficacy. Secondary objectives were to assess the incidence of aGVHD or cGVHD, the incidence of graft failure, progression-free survival (PFS), overall survival (OS), and safety.

Enrollment started on January 2007. A planned safety interim analysis was run by the Independent Review Board on March 2009 after the enrollment of the first 10 patients. There were no unexpected or severe toxicities. The last patient was enrolled on May 2010. We originally planned to enroll 25 patients, but due to a slow enrollment rate, mainly caused by changes in the therapeutic scenario of MM, after 19 patients the study was closed. Follow-up was updated to August 2012. OS was calculated from the time of enrollment to death of any cause. PFS was calculated from the day of enrollment to the day of relapse or progression or death of any cause. The comparison of PFS according to cGVHD occurrence was calculated from the day of the first DLI. OS and PFS were estimated by Kaplan-Meier method, and groups were compared by log-rank test. Response duration times were compared by Welch 2-sample t test. All tests were 2-sided. All the analysis were carried out using R software, version 2.14.1.

RESULTS

Efficacy of Bortezomib-Dexamethasone Followed by DLIs

The median follow-up of alive patients is 40 months (range, 29 to 68 months). Median duration of the full treatment was 201 days (range, 21 to 401 days). Seventeen of

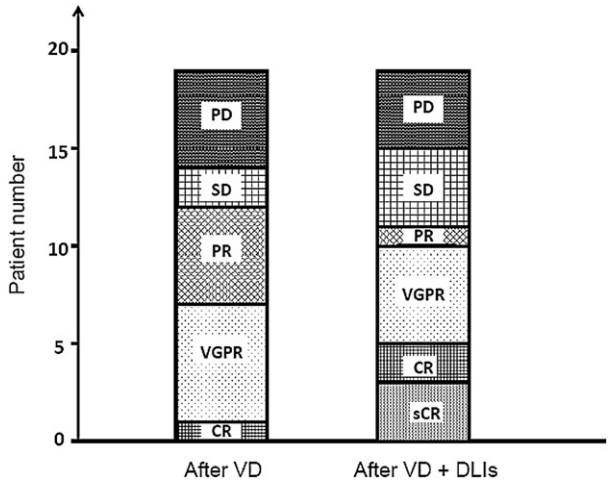

Figure 1. Upgrade of response between VD and DLI phases.

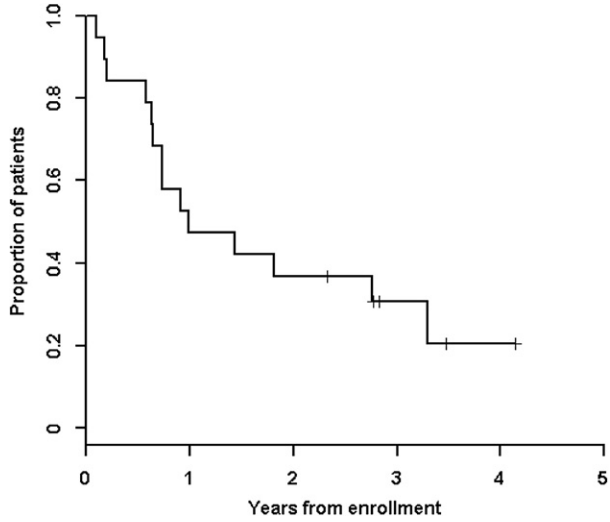

Figure 2. Progression-free survival curve.

19 patients received the 3 planned VD courses. One patient interrupted the treatment after the first VD for disease progression and 1 after 2 courses for the same reason. The overall response rate (RR) after the VD phase was 62%: 1 CR (5%), 6 very good partial remissions (VGPRs) (31%), 5 partial remissions (PRs) (26%), 2 stable disease (SD) (10%), and 5 progressive disease (PD) (26%) (Figure 1).

Two weeks after the last VD course, 16 patients started the DLI program and 3 patients did not, 2 because of disease progression and 1 for refusing to continue treatment. One patient (6%) received only the first DLI due to aGVHD occurrence. One patient received only the first 2 DLIs due to PD. Six patients received three DLIs, due to PD (2 cases, 12%), consumption of donor lymphocytes (1 case, 6%), and achievement of the best response (3 cases, 18%). Eight patients (50%) received the 4 planned DLIs. The overall RR to the DLI phase was 68%: 3 stringent CRs (sCRs) (19%), 2 CRs (13%), 5 VGPRs (31%), 1 PR (6%), 4 SDs (25%), and 1 PD (6%). The overall RR to the entire program was 58%: 3 sCRs (16%), 2 CRs (11%), 5 VGPRs (26%), 1 PR (5%), 4 SD (21%), and 4 PDs (21%) (Figure 1).

Survival Outcomes

Two- and 3-year PFS rates were 37% and 31%, respectively (Figure 2, median PFS, 11.9 months). Two- and 3-year OS rates were 79% and 73%, respectively (Figure 3, median OS not reached). Although the depth of response to the VD courses did not translate into a better survival, patients developing cGVHD after DLI had a superior PFS rate compared with those without cGVHD ($P = .04$, median PFS was 37 versus 8 months after the start of DLI). Two-year PFS after the start of DLIs was 80% for patients developing cGVHD compared with 18% for those without it ($P = .02$). There were no differences in terms of OS between these 2 groups.

Median response duration to VD plus DLI was 17 months (range, 4 to 46 months). Patients developing cGVHD had a median response duration of 29 months (range, 19 to 38 months), which was significantly longer ($P = .01$) than the one observed in patients without cGVHD (median, 8 months; range, 4 to 46). There was no significant difference in the duration of response between patients achieving CR or VGPR after the 3 VD courses compared with those achieving PR or less (median, 22 months versus 17 months, respectively, $P = .83$). Patients achieving sCR, CR, or VGPR after the DLI phase had a longer duration of response than those achieving PR or less (21 versus 11 months), but this difference was not statistically significant ($P = .28$), probably due to the limited number of patients. Median number of lymphocytes infused was 3×10^7 CD3+/kg, and no correlation between T cell dose and aGVHD or cGVHD occurrence or response was observed.

Median time from alloSCT to relapse was 4.6 years. Patients relapsed after 4 years post-alloSCT had a better PFS rate than patients relapsed earlier (not reached versus 7 months, $P = .077$). Median OS of patients relapsed before and after 4 years post-alloSCT was not reached in both groups.

Toxicity Assessment

Bortezomib or dexamethasone dose reductions were performed in 5 patients (26%) for infections (n = 1), pre-existent aseptic necrosis of femur (n = 1), and neuropathy (n = 3). Hematologic toxicities were mild: 2 patients (10%) experienced grade 2 thrombocytopenia. Six patients (31%) developed grade 1, 3 (16%) grade 2, and 2 (10%) grade 3 peripheral neuropathy. Six patients (32%) developed grade

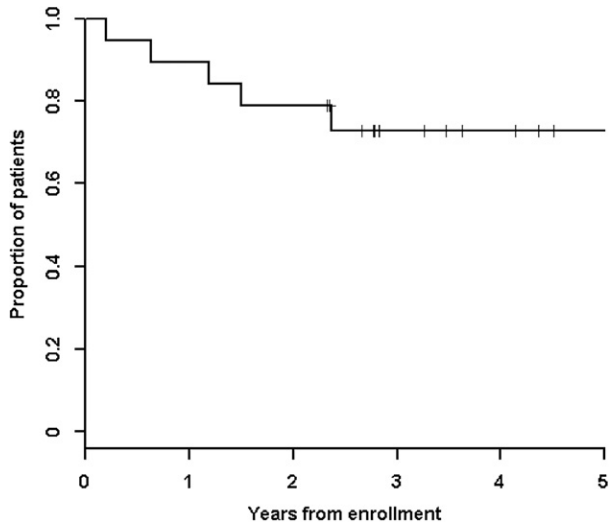

Figure 3. Overall survival curve.

Table 2
Adverse Events

Events	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	1 (5%)		1 (5%)	
Peripheral sensory neuropathy	6 (32%)	3 (16%)	2 (11%)	
Neuralgia		5 (26%)		
Diarrhea	3 (16%)			
Muscle cramps	2 (11%)			
Constipation	2 (11%)	1 (5%)		
Anorexia	1 (5%)			
Infections	6 (32%)	5 (26%)	1 (5%)	
Renal failure	1 (5%)	4 (21%)		
Asthenia	3 (16%)	2 (11%)	1 (5%)	
Rash	4 (21%)			
Hypotension				1 (5%)
Dyspnea		2 (11%)		

1 infections, 5 (26%) grade 2, and 1 (5%) grade 3. Despite the antiviral prophylaxis, 2 patients developed herpetic infections, 1 herpes zoster reactivation, and 1 herpetic keratitis. In 2 cases, grade 2 neuropathic pain was associated with peripheral neuropathy. We did not observe a correlation involving the elapsed time between suspension of immunosuppression and the beginning of bortezomib and the appearance of neuropathy. Other toxicities are summarized in Table 2. After DLIs, 5 patients (31%) developed GVHD: 2 patients had grade I and II aGVHD that evolved to limited cGVHD and 3 patients had de novo limited cGVHD. Overall, 5 limited cGVHD were observed, characterized by oral lichen in 3 patients, xerophthalmia in 1 patient, and xerophthalmia plus lichen in the remaining patient. No patient developed extensive cGVHD. No post-DLI bone marrow aplasia nor deaths due to the treatment were observed.

Chimerism, Immune Reconstitution, and Minimal Residual Disease

Donor chimerism at study enrollment was >95% in all patients, and there were no changes during the treatment. Mean CD16+/CD56+ count was 180/μL at study enrollment, 180/μL before DLIs, 140/μL at 3 months after DLIs, and 110/μL at 12 months after DLIs. This difference was statistically significant ($P = .02$). No other significant differences were observed. Mean CD3+/CD4 + count was 190/μL at study enrollment, 310/μL before DLIs, 360/μL at 3 months after DLIs, and 350/μL at 12 months after DLIs. Mean CD3+/CD8 + count was 320/μL at study enrollment, 310/μL before DLIs, 280/μL at 3 months after DLIs, and 330/μL at 12 months after DLIs. Mean CD19+ count was 170/μL at study enrollment, 120/μL before DLIs, 140/μL at 3 months after DLIs, and 110/μL at 12 months after DLIs. Bone marrow samples for minimal residual disease monitoring were available for 5 patients who achieved at least 1 CR, but in none of these was it possible to generate the patient-specific molecular marker.

DISCUSSION

Bortezomib is an effective treatment for relapsed myeloma, but, at present, the data on its use after alloSCT are few and derived only from retrospective series. We prospectively evaluated the sequential use of VD and DLIs in a phase II study including patients relapsing or progressing after alloSCT. The overall RR following VDs was 62% and after DLIs was 68% (Figure 1). The 3-year PFS and OS rates were 33% and 78%, respectively. In a retrospective analysis conducted by Hoevenaren and colleagues [19], 30 MM patients received a median of 4.4 bortezomib courses for persistent or relapsed disease after alloSCT, and 21 also received escalating DLIs after the first 2 or 3 bortezomib courses. The RR to the entire treatment was 60%, with a median PFS rate of 12.7 months. The overall RR observed in our and the Hoevenaren studies are similar and are consistent also with the RR of 61% of a rather heterogeneous European retrospective analysis on 23 patients [20]. These favorable clinical responses suggest the existence of a synergistic activity between bortezomib and the GVM effect. In this sense, preclinical data have shown that bortezomib has immunomodulatory effects, through activating TRAIL/DR5-mediated killing [12], strengthening the natural killer anti-MM activity [13], and promoting antigen spreading by increasing immunogenicity of the dying cells [14].

Overall, the DLIs were well tolerated; in particular, we did not observe an excess of aGVHD and cGVHD, as only 5 patients developed limited cGVHD. DLIs have led to a significant upgrade of response, in particular in terms of depth of remission (Figure 1). Although after VD only 1 patient was in CR and 6 in VGPR, after DLIs 3 patients achieved sCR, 2 CRs, and 6 VGPRs. This is a remarkable finding if compared with DLIs alone, which usually induce responses in the range of 30%, with a low rate of CR [1].

The lack of severe aGVHD exacerbation can be explained both by the combination with dexamethasone and by the immunomodulatory properties of bortezomib. Taking advantage of this property, Koreth et al. designed a reduced-intensity conditioning regimen including early bortezomib administration after transplantation, showing promising results in terms of low incidence of aGVHD and cGVHD and suggesting that bortezomib is a promising immunomodulatory agent in the setting of alloSCT [21,22].

As reported by others [23,24] as well as in our study, we observed a correlation between cGVHD occurrence and PFS, supporting the concept that the GVM effect is a key component of alloSCT and might be an important component in long-term disease control. Interestingly, this finding is in line with previous studies [25] and supports the hypothesis that bortezomib may be favorably combined with DLIs. It should be noted that patients who had a later relapse after alloSCT responded better to the study treatment, with a superior PFS. This suggests that an indolent disease facilitates the activity of bortezomib and DLIs, because it is well known that the disease kinetic affects the graft-versus-tumor efficacy [26].

In our study, toxicities were mild, and no unexpected grades 3 to 4 side effects were observed. Despite the antiviral prophylaxis, 2 patients developed herpetic infections: 1 herpes zoster reactivation and 1 herpetic keratitis, emphasizing the increased susceptibility of bortezomib-treated patients to herpetic infections [27] and the necessity of an adequate prophylaxis. Only 2 patients developed grade 3 peripheral neuropathy. In a previous retrospective study focused on the incidence of bortezomib-related peripheral neuropathy, an increased risk of this disabling complication was observed in alloSCT patients, with 29% of patients experiencing a grade 3 to 4 neuropathy, and 25% required bortezomib discontinuation for this problem, despite dose reduction [28]. In this analysis, a correlation between severe neurotoxicity and cyclosporine treatment was observed. In our study, all patients were off treatment by immunosuppressive therapy for at least 5 weeks before enrollment and were therefore protected from any cyclosporine-related effect on peripheral neuropathy.

In conclusion, we demonstrated the feasibility of the VD treatment followed by a program of escalating DLIs. This combination was safe, well tolerated, may be effective, and seems to optimize the GVM effect.

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Authorship Statement: P.C., V.M., F.S., and P.V. participated in the conception of the study; P.C., V.M., F.S., and P.V. were responsible for the study design, V.M., F.S., F.P., M.O., B.B., A.M., A.S., A.D., and R.F. were responsible for the acquisition of data; F.S. and P.V. were responsible for the statistical analysis; F.S. and V.M. were responsible for the entire Results section, including figures and tables; V.M. was responsible for writing the Introduction and Discussion sections; F.S. was responsible for writing the Methods and Results sections; and P.C. was responsible for writing the overall article.

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